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PATENT ABSTRACTS OF JAPAN

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(54) PASTE PREPARATION

(57)Abstract:
PURPOSE: Pharmacologically active ingredients are added to the tackifying base which is composed of an A-B-A type thermoplastic block copolymer, natural or synthetic rubber, oil and tackifier to give paste preparation giving good feel on application and releasing the active ingredients into skin smoothly.
CONSTITUTION: Preferably, 100pts.wt. of A-B-A type thermoplastic block copolymer, 5W400pts.wt. of natural rubber and/or synthetic rubber other than the above-cited such as isoprene rubber or butyl rubber, 20W300pts.wt. of oil such as paraffin or higher fatty acid ester and 50W400pts.wt. of a tackifier such as rosin or petroleum resin are kneaded together to prepare a tacky base. The base is combined with a pharmacologically active ingredient such as anti-inflammatory analgesic agent and spread on a support to give a paste preparation. The base has high compatibility with pharmacologically active ingredients and gives a paste with high adhesion to skin, good releasability, high resistance to sweat and good releasability of the active ingredients.

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1.Title of the invention

Paste Preparation

2.Claims

(1) A patch in which an tackifying base composed of A - B - A type thermoplasticity block copolymer gum, natural rubber and /or synthetic rubber aside from the above, oil, and tackifier and a drug ingredient component added is spread on support.

(2) A patch as claimed in claim 1 in which synthetic rubber is one or more selected from isoprene rubber, butyl rubber, butadiene rubber, styrene-butadiene rubber, ethylene-propylene rubber group.

(3) A patch as claimed in claim 1 in which oil is one or more selected from paraffin oil and/or higher fatty acid ester group.

3. Detailed description of the invention

The present invention relates to the paste preparation in which skin adhesive force was done well by keeping the balance of physics characteristic between each component, and pain and skin - fit in exfoliation are controlled as much as possible as well.

As matrix of paste preparation, the thing which combined thermoplasticity rubber-like substance such as natural rubber, isoprene rubber, neoprene gum with tackifier resin such as rosin, ester gum and drug efficacy constituent such as antiphlogistic analgetic is employed conventionally.

In these paste preparation, stickiness and skin adhesive property is superior, but on the other hand, because spreading nature of a drug efficacy ingredient is bad, a method to add oil of liquid paraffin is adopted. However, remarkable depression of cohesive power is invited, there was a case to show unfavorable resultant such as leak during storange or paste remainders to application skin face after exfoliation.

In addition, in late years, as an improvement type of the patch, the patch which employed thermoplasticity block copolymer gum as a substitute of thermoplasticity rubber-like substance is spread.

For example, these patch, it is disclosed many such as a Japanese Patent Laid-Open No. 54-138124 bulletin, a Japanese Patent Laid-Open No. 55-35633 bulletin, a Japanese Patent Laid-Open No. 55-133310 issue bulletin, a Japanese Patent Laid-Open No. 55-141408 issue bulletin, a Japanese Patent Publication No. 56 - 12613 issue bulletin, a Japanese Patent Laid-Open No. 56-18916 issue bulletin, a Japanese Patent Laid-Open No. 56-20515 issue bulletin. However, when pasting was applied to skin face for long time, there was a case to fall off of patch in application because of short in perspiration resistance adhesion, although cohesive of base material seemed to be improved.

Furthermore, the manipulation which lowers heat temperature and base substance of large thermoplasticity are required in manufacture, from a point of view to control damage of a drug efficacy ingredient to contain in patch, such as thermal decomposition or loss by fugacity during application,

therefore balance of physics characteristic such as cohesive power, adhesive force became bad.

As a result of present inventors should have broken off the prior-art weak point, and having repeated a study zealously, the present invention was reached, that thermoplasticity block copolymer gum having configuration of specify and natural rubber and / or synthetic rubber aside from the above is mixed, and oil and drug efficacy constituent are added has moderate thermoplasticity and exfoliation resistance correction function to skin to affix it to, therefore, discharge nature caused by spreading build-up of drug constituent improves remarkably.

The present invention provides the paste preparation in which drug efficacy constituent component is added to the tackifying base composed of A - B - A pattern thermoplasticity block copolymer gum, natural rubber and / or synthetic rubber aside from the above, oil and tackifier is spread on support A - B - A type thermoplasticity block copolymer gum used for the present invention is copolymer gum of A - B - A type configuration comprising of hard polymer A and flexible polymer B, and the A - B - A pattern star radial block copolymer gum which made by binding A - B - A pattern tele block copolymer gum and flexible polymer B of A - B pattern block copolymer with coupling agent can employ.

An A block is hard polymer of vinyl compound such as styrene, methylstyrene, and, polymer having weight average molecular weight in the range of about 1,000-500,000 with the glass transition temperature of more than 70 degrees Celsius is effective.

A B block is soft polymer of the conjugated diene compound such as butadiene, isoprene, and polymer having weight average molecular weight in the range of about 4,500-1,000,000 with the glass transition temperature of - 100-30 degrees Celsius is effective.

As for the end A block of the thermoplasticity block copolymer gum, about 5 - 65 % by weight of the copolymer resin is employed.

Natural rubber and / or synthetic rubber used along with the copolymer gum give perspiration resistance adhesion and good skin adhesive property held for long time to paste preparation of the present invention. For example, natural rubber or synthetic rubber such as isoprene rubber, butyl rubber, butadiene rubber, styrene-butadiene rubber, ethylene-propylene rubber, chloroprene rubber, neoprene gum is given, and combined in the range of about 5-400 part by weight as against the A - B - A pattern thermoplasticity block copolymer gum 100 part by weight is desirable, and these can be chosen by type and quantity of employing gum, oil, tackifier appropriately.

A material employed as an oil ingredient in the present invention is oil of liquid in room temperature having compatibility with flexible polymer B of the A - B - A pattern thermoplasticity block copolymer gum, and non-compatibility with rigid polymer A, machine oil, cylinder oil, trans oil, rosin oil, various liquid paraffin oil are used preferably. The mixture which is provided by adding substance presenting oily by means of heat such as paraffin wax or low molecular weight polyethylene having melting point of less than or equal to 120 degrees Celsius, to the above oil constituent can be used.

In addition, as for these oil ingredients, a thing having high boiling (more than a melting point of adhesive base) and low volatility is used preferably for restraint of damage by heat when paste preparation of the

present invention is produced.

As amount of the oil, 20-300 part by weight as against A - B - A type thermoplasticity block copolymer gum 100 part of weight is desirable. There is the case that spreading nature of drug efficacy constituent to contain is bad, and it is not got desirable drug efficacy when the amount is less than 20 part by weight.

In addition, when the amount is more than 300 part by weight, blooming of oil ingredient in conservation brings unfavorably depression of skin adhesive property in pasting.

Higher fatty acid ester as natural product such as animal wax of lanolin or plant wax of carnauba wax or, synthesis higher fatty acid ester synthesized by aliphatic acid of C 8 - C 22 and ethyl alcohol of C 1 - C 17 such as diisopropyl adipate, ethyl laurate can be used as oil in the present invention aside from the liquid paraffin.

As tackifier of the present invention, rosin, degeneration rosin, petroleum system resin, cumarone indene resin, methylindene resin, polyterpene resin, PS resin are given, and in consideration of adhesive force to skin, rate of 50-400 part by weight seems as against the A - B - A pattern thermoplasticity block copolymer gum 100 part by weight is desirable.

When paste preparation of the present invention is produced, mixture of appointed rate of the A - B - A type thermoplasticity block copolymer gum, natural rubber and / or synthetic rubber aside from the above, oil and tackifier is kneaded enough under heat of dimension having flowability, the oiliness gel-shaped slime which has hyperviscosity in room temperature degree and no flowability is prepared.

The process of adding drug efficacy constituent or its solution prepared in a predetermined ratio to the slime provided is done desirably in temperature field of less than or equal to about 70 degrees Celsius in order to prevent loss of drug constituent.

As a drug efficacy ingredient used in the process, antiphlogistic analgetic used for normal fomentation such as for example, methyl salicylate, salicylic acid monoglycol, l- menthol, camphor, capsicum extract, mustard oil, scopolia extract, and ,Japanese belladonna extract is used preferably. As other drug efficacy ingredient, nonsteroid strainanti-inflammatory agent such as indometacin, diclofenac sodium, steroid strain anti - inflammatory agent such as dexamethasone, fluocinolone acetonide, hydrocortisone, bactericide such as acrinol, hexidine gluconate, crude drug such as lithospermum root, ligusticum root. These combination quantity can choose that in the quantity which is pharmacologically effective.

In addition, the drug efficacy ingredient can be used in combination of two or more by purpose and application.

The adhesive matrix which contained a provided drug efficacy ingredient come to oiliness gel-shaped by cooling it to room temperature field after spread on support having plasticity, and paste plaster of a drug efficacy constituent component is provided.

As for the support used for the present invention, cloth of flannel or a thick nonwoven fabric foaming film used as support for fomentation conventionally are used both, and, in these other, synthetic resin film can be employed.

Various additive which are usually used for example, preservation antifungal agent such as thymol, boric acid can be added to the paste preparation in

an arbitrary process of production according to need.

In the paste preparation of the present invention, there is a little fugacity of drug efficacy constituent with time because adhesive base is superior in compatibility with the drug efficacy ingredient and percutaneous absorption velocity and absorbed dose in use are increased by function of oil constituent so that enough pharmacological effect is provided, and an advantage to have the binding capacity in moderation is provided.

In addition, balance such as skin adhesive property, perspiration resistance adhesion, a pain in exfoliation, cohesive power shows effect to become good in extremely by combination of A - B - A type thermoplasticity block copolymer gum and natural rubber and or / synthetic rubber aside from the above at the rate of specify.

Furthermore, water-containing gel-shaped emulsion-type patch of W/O pattern can be prepared by adding aqua in the range of about 5-70 % by weight in the patch for purpose of giving cold sensation or improving spreading nature of a drug efficacy ingredient in a manufacture process.

The present invention is , explained more to be concrete by Example shown in the following, but, not limited to these.

Part means part by weight.

Example

Sample No. 1 and 2 were made by adding mixed agent of table 2 to compound shown in table 1 as compound example I and I I, reference sample No. 1 and 2 are made by adding mixed agent shown in table 2 to compound in table 1 as referance example I and II. In this way, paste preparation were provided.

It was shown in examination result table 3 and table 4.

In manufacture of sample No.1 and 2, alkylation bisphenol as age resistor was added to styrene - isoprene - styren block copolymer (S - 1 - S) , masticated at 140 degrees Celsius in compression kneader for five minutes , isoprene rubber (IR) or styrene-butadiene rubber (SBR) was added and kneaded in the temperature for five minutes.

After liquid paraffin and Polybutene were added and mixed uniformly, petroleum resin is added and mixed enough uniformly. When temperature of mixture was lowered to 70 degrees Celsius, mixed agent was added, and binding capacity base of the drug component that was uniformity was got.

It was spread on a nonwoven fabric next in about 70 degrees Celsius temperature by a calender roller , quench was done, and the samples ware got.

In manufacture of reference sample No. 1, alkylation bisphenol as age resistor was added to S-I-S , masticated at 140 degrees Celsius in compression kneader for 10 minutes, reference sample was got in same manipulation and temperature condition as a manufacture method of sample No. 1 except that natural rubber or synthetic rubber was removed.

In manufacture of reference sample No. 2, age resistor was added to IR, masticated at 170 degrees Celsius in compression kneader for 10 minutes, reference sample was got in same manipulation as a manufacture method of sample No. 1 except that gum rosin was added instead of petroleum resin and except S-I-S and liquid paraffin under temperature of 120 degrees Celsius.

Table 1

compound	combination
S - I - S	I 100, II 100, reference example I 100, reference example II -

SBR I -, II 50, reference example I -, reference example II -
IR I 200, II -, reference example I -, reference example II 100
Liquid paraffin I 100, II 100, reference example I 50, reference example II -
Polybutene I 50, II 50, reference example I 10, reference example II 30
Petroleum resin I 200, II 200, reference example I 80, reference example II -
Gum rosin I -, II -, reference example I -, reference example II 100
Age resistor I 0.7, II 0.4, reference example I 0.3, reference example II 0.3
Mixed agent I 72, II 41, reference example I 27, reference example II 26

The abbreviated designation and the attribute or structure in table 1 are as follows.
S-I-S; styrene - isoprene - styrene tele plotter elastomer
Mean molecular weight 125000
Styrene / rubber rate 14/86
Melt index (G condition) 10g / min
Solution viscosity (25 degrees Celsius, 26Wt %, toluene solution) 1600 cps

IR: isoprene rubber
Trade name KURAPRENE IR - 10 (Kuraray company)

SBR: styrene— butadiene rubber
Trade name JSR1013N (Japan Synthetic Rubber company)
Liquid paraffin: Specific gravity (15/4 degrees Celsius) 0.83
Coefficient of viscosity (37.8 degrees Celsius) 9.5cat.
Polybutene: Mean molecular weight 1260
Kinematic viscosity (210 · F) 32000cat.
Specific gravity (15/4 degrees Celsius) 0.895
Petroleum resin: Alicycle type saturated hydrocarbons resin
Mean molecular weight 630
Softening point 90
Acid number 0
Gum rosin: China gum rosin
Softening point 95-105 degrees Celsius
Age resistor: Alkylated bisphenol

Table 2
Mixed agent
The ratio
Methyl salicylate 10
Salicylic acid thing glycol 5
l- menthol 10
dl- camphor 5
Thymol 2
Result of practical use test evaluation of paste preparation of the present

invention and reference sample were shown in table 3.

Table 3

A practical use test	
Adhesive property	
Sample 1	good
Sample 2	good
Reference sample 1	weak
Reference sample 2	good
pain in abrasion	
Sample 1	good
Sample 2	good
Reference sample 1	good
Reference sample 2	pain
A paste remainder to skin	
Sample 1	Nothing
Sample 2	Nothing
Reference sample 1	Nothing
Reference sample 2	Nothing
Drug effect intensity	
Sample 1	good
Sample 2	good
Reference sample 1	good
Reference sample 2	good
Drug effect time (hr)	
Sample 1	6
Sample 2	5
Reference sample 1	6
Reference sample 2	7
Time before beginning to work (minute)	
Sample 1	5>
Sample 2	5>
Refrence sample 1	5>
Refrence sample 2	20
Skin perspiration resistance adhesion time(hr)	
Sample 1	2<
Sample 2	2<
Reference sample 1	0.5
Reference sample 2	2<

In table 4, the measurement (determination) of content of a drug efficacy ingredient in patch after pasting up into human body side for six hours is shown.

Table 4
A drug efficacy ingredient
Methyl salicylate Sample 38, Sample 2 32, Reference sample 1 36, Reference sample 2 62
Salicylic acid mono glycol Sample 1 31, Sample 2 25, Reference sample 1 29, Reference sample 2 47

(quantitative method out of table 4)
1g of adhesive base comprising drug ingredient component and spread to patch is soused in ethanol 50ml of an internal standard component, and shaked and extracted for 3 hours at 40 degrees Celsius. For the sample solution provided in this way, assay was done in high performance liquid chromatography.
In addition, content of drug efficacy constituent before it was put in human body skin was calculated as 100%.
Paste preparation of the present invention has good skin adhesive property, exfoliation nature, perspiration resistance adhesion as is apparent from the Example, and discharge nature to skin of drug efficacy constituent is better, having immediate effectivity and the durability, it was superior.